## REMARKS

Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 are present for purposes of prosecution. All of the above claims are rejected.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

### Amendments to Claims

Independent Claims 37, 58, 59, 60, 71, 72 and 73 have been amended to include the glyburide particle size distribution of at most 25% of the particles are less than 11 μm and at most 25% of the particles are greater than 46 μm. Accordingly, the mean particle size present is between 11 μm and 46 μm.

Bauer et al. disclose a mean glyburide mean particle size of ±5 μm which is outside the scope of the mean particle size claimed herein.

### Claim Rejections - 35 U.S.C. §112

The Examiner mentions that

> "The phrase 'drug naïve patient' renders the claims indefinite because the claim includes elements not actually disclosed which could mean the 'drug naïve patient' is 'a patient who has not received any drug', thereby rendering the scope of the claim unascertainable. See MPEP §2173.05(d). The 'type 2 diabetes' in the preamble of the claims may be implied as being what is meant for the 'drug' of treatment but this is implied at best. An implied limitation is not clear and concise as required under §112, second paragraph."

The term "drug naïve patient" refers to a patient who is to receive the drug as first line therapy for treatment of diabetes or related disease or condition as claimed herein. It would be apparent to those skilled in the art that the drug naïve patient does not refer to a patient who has never received any drug of any kind for any purpose. However, in order to make the claims more certain, the claims have been amended to indicate that the drug naïve patient is a patient who has had no previous oral hyperglycemic treatment or no such treatments for 2 months (see page 25, lines 36 and 37 of the Specification).

Discussion of Invention

Applicant's invention as claimed is defined as a method for

1) first line treatment of diabetes

2) in a drug naïve patient

3) wherein a low dose of a combination of metformin and glyburide is administered

4) so that daily dosage of metformin is 750 mg or less, and

5) where the glyburide has a special particle size distribution of at most 10% of the particles are less than 11 μm and at most 10% are greater than 46 μm.

The essence of Applicant's method is to employ a maximum daily dosage of 750 mg metformin together with the glyburide of special particle size distribution to achieve equivalent efficacy as compared to efficacy achieved with prior art dosing, but with reduced side effects as compared to that observed with prior art dosing. See page 41, lines 5 to 35 of the Specification.

It is submitted that Applicant's method as claimed is patentable over the combination of the cited Barelli et al. patent and Bauer et al. patent.

Claim Rejections - 35 U.S.C. §103

Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barelli et al. (WO 97/17975, pub. date: May 22, 1997, equivalent to US Patent 5,922,769) in view of Bauer et al. (US Patent 5,258,185, issue date: Nov. 2, 1993).

The Examiner contends that:

> "Claims 37, 45-54, 58-60, 71-73, and 75-79 are directed to a method of treating type 2 diabetes comprising administering to a drug naïve human patient, as first line therapy, a low dose of a combination of metformin and glyburide where the daily dosage of metformin is about 160 mg to about 750 mg; the daily dosage of glyburide is about 0.5 mg to 15 mg. Further limitations include: metformin and glyburide is formulated as a single dosage form (claim 45); weight ratio of metformin and glyburide is from about 400:1 to about 50:1 (claim 46); and that the glyburide having particular particle distributions and the patient population being drug naïve patients as recited in the claims."
>
> "Barelli et al. teach a combination of 500 mg metformin and 5 mg glibenclamide (glibenclamide and glyburide are synonymous) being useful for the treatment of type II diabetes (column 3, lines 14-17) and that the combination makes the therapeutical effect optimum at any time of the progression of the disease, starting

from minor cases to the most severe ones (column 3, lines 19-21). Barelli et al. also disclose that the weight ratio of metformin and glibenclamide is 200:1 (column 2, lines 18-20) which overlaps with the claimed weight ratio. Barelli et al. further teach a single coated tablet in EXAMPLE 1 (column 9, lines 25-26) which contains 500 mg metformin and 5 mg glibenclamide."

The Examiner further states that:

"The difference between Barelli et al.'s teaching and the instant claimed invention lies in that Barelli et al. do not teach (i) glyburide having particular particle distributions and (ii) the patient population being drug naïve patients."

Barelli does not teach or suggest employing low dose metformin which is the essence of Applicant's invention.

The Examiner further maintains that:

"However, Bauer et al. teaches pharmaceutical formulations of glibenclamide rapidly releasing the active substance for the treatment of diabetes (see abstract). Bauer et al. disclose improved drug release and bioavailability (column 2, lines 17-22) of the drug glibenclamide by using a preparation having micronized glibenclamide with mean particle size of ±5 μm which overlaps with the instantly claimed particle size of 2-60 μm. Therefore, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare micronized glibenclamide for the combination of metformin and glibenclamide as disclosed by Barelli et al. in view of Bauer et al. to result in the drug combination of the instant invention, motivated by Bauer et al. that glibenclamide is virtually water-insoluble (column 2, line 9) and micronized glibenclamide improves its solubility and bioavailability (column 2, lines 31-32). . . .

"With respect to the recitation of metformin dosage being 250 mg, glyburide dosage being 1.25 mg of claims 50, 53, 54, 58, 59 and 79, although Barelli et al. do not explicitly teach this particular dosage, Barelli et al. have provided guidance that 1500 mg metformin and 15 mg glyburide are the maximum recommended daily dosage in the combination (column 3, lines 37-40) with recommended weight ratio of 200:1 (column 2, line 20) between metformin and glyburide. The determination of the appropriate dosage amounts of active ingredients for a treatment is routinely made by those of ordinary skill in the art and is well within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information of the active ingredient disclosed in the prior art. Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to determine the amount of metformin and the amount of glyburide for achieving the effect of treating type 2 diabetes to result in the pharmaceutical composition as claimed with a reasonable expectation of success."

Barelli et al. disclose tablets containing a combination of 500 mg metformin and 5 mg glyburide for treating diabetes, so as to allow a daily dosage of 1500 mg metformin and 15 mg glyburide (column 2, lines 64 to 67). Barelli et al. teach that its tablets provide medicament for treating diabetes "in cases of secondary failure to a combination glibenclamide-metformin used in therapy [that is, 500 mg metformin / 2.5 mg glibenclamide or a ratio of 200:1 or 400 mg metformin / 2.5 mg glibenclamide or a ratio of 160:1]." The Barelli et al. combination is 500 mg metformin / 5 mg glibenclamide or a 100:1 ratio to achieve good efficacy with minimal side effects.

However, Barelli et al. has nothing to do with Applicant's inventive concept as claims.

1) The Barelli et al. combination is for patients who have previously failed on a combination of metformin and glyburide. Barelli et al. does not relate to first line treatment.

2) The patients employed in the Barelli study are not drug naïve patients as required in Applicant's method.

3) Applicant's method requires treating with a low dose combination of metformin (a maximum 750 mg daily) and glyburide.

4) Barelli et al. does not disclose or suggest using a low dose of metformin. Until Applicant's invention no one used a low dose of metformin, that is a maximum of 750 mg daily for treatment of diabetes. It therefore has to be presumed that Barelli et al. is not implicitly or otherwise suggesting to use a low dose of metformin, that is 750 mg or less.

5) Barelli et al. makes no mention of particle size distribution of glyburide. Applicant's method requires a specific particle size distribution of glyburide not disclosed or suggested in Barelli et al.

In view of the above, it is quite clear that Applicant's method as claimed is neither disclosed nor suggested by Barelli et al.

Applicant's method as claimed is also patentable over a combination of Barelli et al. and Bauer et al. As indicated, Barelli et al. does not disclose or suggest use of low dose metformin (160 to 750 mg daily) in drug naïve patients for first line therapy but only in secondary failure patients. Barelli et al. is devoid of Applicant's inventive concept of use of a combination of low dose metformin (maximum of 750 mg) and specially size glyburide in first line treatment of drug naïve patients. Even if Barelli et al. is taken with Bauer et al., the resulting combination would not make Applicant's method obvious since neither reference discloses or suggests use of low dose metformin

or treatment of drug naïve patients in first line therapy or use of specifically sized glyburide having a mean particle size of greater than ±5 μm.

It is submitted that Applicant's invention is claimed as patentable over Bauer et al.

U.S. Patent No. 5,258,185 to Bauer et al. discloses in Col. 2, lines 17 to 20,

> "microionized, i.e. finely comminuted, glibenclamide (mean particle size ±5 μm) showed an improved drug release and bioavailability above all in the presence of tensides . . ."

There is no disclosure or suggestion in Bauer et al. of a method of treating diabetes in a drug naïve patient employing a low dose of a combination of metformin and glyburide. Bauer et al. discloses formulations containing glyburide but not metformin. In addition, the glyburide employed in Applicant's invention as claimed will have a mean particle size greater than ±5 μm. Accordingly, it is clear that Applicant's invention as claimed is patentable over Bauer et al.

The Examiner further maintains that:

> "Claims are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23 and 44 of U.S. Patent No. 6,660,300 [to Timmins et al.]. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented invention makes obvious the instant invention."

> "The patented invention is directed to a method of administering the same combination of metformin and glyburide as that of the instantly claimed invention for treating diabetes which includes overlapping patient population of the type 2 diabetic patients in the instant invention. Therefore, the patented invention makes obvious the instant invention."

The Timmins et al. patent discloses and claims a biphasic controlled release delivery system for metformin alone or in combination with another pharmaceutical including glyburide. Timmins et al. in Claims 23 and 44 claim a combination of metformin and glyburide in the biphasic controlled release delivery system.

Timmins et al. does not disclose or suggest Applicant's inventive concept. There is no disclosure or suggestion in Timmins et al. of treating a drug naïve patient (first line therapy) with low dose metformin and specially sized glyburide as discussed above and as claimed herein. Accordingly, it is clear that Applicant's invention as claimed is patentable over Timmins et al.

In view of the foregoing, it is submitted that Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 overcome all formal objections and are patentable over all cited art taken in any combination and therefore are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000

Date: April 10, 2007

Burton Rodney
/burton rodney/
Attorney for Applicant
Reg. No. 22,076
Phone: 609-252-4336